## Residual solvents determination in pharmaceutical products by GC-HS and GC-MS-SPME.

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Solid-phase microextraction (SPME) has been applied to the residual solvents determination in pharmaceutical products and was compared with the static headspace. Three fibers with different polymer films were compared and the polydimethylsiloxane/divinylbenzene coated fiber was found to be the most sensitive for the analyzed analytes. Between the investigated sample preparation techniques, gastight-SPME proved to be the most sensitive, with DL values ranging from 5 pg ml(-1) to 2 ng ml(-1). Headspace SPME is more precise, with RSD of peak areas values ranging from 2 to 3%. The headspace SPME method was successfully validated. The validation data are reported in the text. The most important difference between the two techniques is that the gastight SPME showed better behavior towards very volatile solvents. Compared with the static headspace technique, both SPME methods showed superior results, being compatible with the pharmaceutical samples.

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# Static headspace gas chromatographic analysis of the residual solvents in gel extrusion module tablet formulations

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**Abstract**

A rapid static headspace-gas chromatographic (SHS-GC) method was developed and validated for the quantitation of residual solvents in pharmaceutical gel extrusion module (GEM) tablet formulations. A static headspace sampling technique was utilized to overcome the difficulties imposed by direct injection methods. A Rtx-1701 megabore capillary column was selected to achieve optimal resolution among organic volatile chemicals used commonly in the manufacturing of GEM tablets, residual solvents in the active ingredient and excipients, and other formulation matrix artifacts. A 50-mM pH 3.0 sodium phosphate buffer was used as a sample diluent to minimize matrix effects. The instrumental parameters of the SHS-GC method were optimized for sensitivity and precision. Quantitation was performed by external standard analysis. The SHS-GC method was validated according to regulatory requirements and produced acceptable results with respect to specificity, linearity, range, detection and quantitation limits, precision, and accuracy. 

*Keywords:* Static headspace; Gas chromatography; Gel extrusion module; Residual solvents

## 1. Introduction

Controlled- or sustained-release drug delivery systems have been widely employed to achieve desired therapeutic effects with the advantages of eliminating undesirable side effects, diminishing repeated dosages, and improving biological and pharmaceutical efficiencies. Gel extrusion module (GEM) tablet formulation is a novel controlled-release oral drug dispersion delivery device [1]. The GEM tablet consists of a compressed core prepared from an admixture comprised of a therapeutically effective amount of a beneficial agent, a gel-forming polymer which upon hydration forms gelatinous microscopic particles, and other pharmaceutical excipients. The core is completely coated with a thin water-impermeable, water-insoluble polymeric coating, which contains apertures to expose discrete portions of the surface of the core. In the environment of use, as biological fluid contacts the exposed core surface, hydration of the gel-forming polymer occurs at the surface. As water is absorbed by the polymer particles, gelatinous microscopic particles are formed and

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released from the surface. As a result of the dispersion of gelatinous microscopic particles, the beneficial agent is also released from the tablet core through the apertures into the aqueous environment of use. The release rate of the drug is controlled by the core composition as well as the number and size of the apertures on the polymeric coating.

During the manufacturing process, the GEM tablet formulation product was exposed to several organic volatile chemicals. Ethanol, isopropanol, and acetone are the commonly used granulation media. Methanol may be present in certain grades of ethanol. Ethanol and acetone are also used in the preparation of the polymeric coating of GEM tablets [1]. Isopropanol may be used in the crystallization of the active ingredient while ethyl acetate is a process solvent for the gel-forming polymer [2]. Low levels of these organic solvents are inevitably present in the GEM drug product even after the drying process. Residual solvents, also called organic volatile impurities (OVIs), not only affect physiochemical properties of a drug, such as particle size, dissolution rate and stability, but also can present a serious potential health hazard. Worldwide regulatory authorities all require the reduction of residual solvents to acceptable levels. In the International Conference on Harmonisation (ICH) guideline Q3C 'Impurities: Residual Solvents' [3], methanol is classified as a class 2 solvent with a permitted daily exposure (PDE) limit of 30 mg/day and a concentration limit of 3000 ppm while ethanol, acetone, isopropanol and ethyl acetate are classified as class 3 solvents with PDE limits of 50 mg/day and concentration limits of 5000 ppm. Therefore, it is of critical importance to develop a robust quantitative analytical method for the determination of these residual solvents in the GEM tablet formulations.

Determination of residual solvents or OVIs in drug substances, excipients, and formulated drug products is known to be one of the most difficult and demanding analytical tasks in the pharmaceutical industry. The very complex nature of GEM tablet formulation presents an even greater challenge. The most appropriate method for analyzing organic volatile compounds is gas chromatography (GC). There are generally two sample introduction techniques for the analysis of volatile compounds by GC: direct injection and headspace sampling. While direct injection is simple and does not require specialized hardware, it has several major drawbacks. Injection of non-volatile components causes the contamination of the GC system and the deterioration of the GC column. Degradation of deposited non-volatile components at elevated temperatures in the injection port also interferes with subsequent injections. Consequently, frequent and time-consuming cleaning of the GC system is required. Moreover, sample backflash as a result of the large expansion volume of water results in poor injection reproducibility and poor method precision. Direct injection of the GEM tablet sample also requires a tedious sample preparation procedure. Heating of sample solutions is needed to ensure an efficient extraction of OVIs from the GEM tablet matrix. In addition, a lengthy centrifugation at extremely high centrifugal speed is needed to remove the gelatinous particles so that an injectable sample solution may be obtained for GC analysis. As a result, OVIs are lost during these sample preparation steps, and low recovery is observed. All of these reasons make the direct injection the least desirable sampling technique for use in the analysis of GEM tablet formulations for residual solvents.

Static headspace-gas chromatography (SHS-GC) [4] has become the preferred technique for the analysis of residual solvents in bulk pharmaceuticals [5–10] and finished drug products [11–13] because it offers several advantages over the direct injection technique. In headspace analysis, only volatile components are introduced into the GC system, resulting in extended column lifetime and reduced instrument maintenance. With automated systems, SHS-GC also provides superior sensitivity and reproducibility. SHS sampling is conducted by placing a liquid or solid sample in a sealed vial, which is then thermostated until a thermodynamic equilibrium between the sample and gas phase is reached. A

known aliquot of the gas phase is then transferred to a gas chromatography for analysis. Many factors such as thermostat temperature, equilibration time, sample volume, and sample matrix have significant influence on the quantitative determination of volatile compounds using SHS-GC. Optimization of these parameters can be critical to the development of an accurate SHS-GC method.

In this article, a simple, rapid, and sensitive SHS-GC method for use in quantitating the residual solvents in GEM tablets is described. Specifically, the authors have determined the residual methanol, ethanol, acetone, isopropanol, and ethyl acetate levels in the GEM formulations by external standard analysis. An Rtx-1701 megabore capillary column was selected to achieve the optimal resolution among organic volatile chemicals commonly used in the manufacturing of GEM tablets, residual solvents in both the active ingredient and excipients, and other formulation matrix artifacts. A 50-mM pH 3.0 sodium phosphate buffer was used as a sample diluent to minimize matrix effects. In addition, the validation of the method in accordance with regulatory requirements for the pharmaceutical industry is described.

## 2. Experimental

### 2.1. Reagents and chemicals

GEM tablets were obtained from the Pharmaceutical Research and Development department of Merck Research Laboratories (West Point, PA). Solvents used were of ≥ 99% purity and were purchased from the following sources: methanol, acetone, isopropanol, ethyl acetate, acetaldehyde, *N,N*-dimethylformamide (DMF) from Fisher Scientific (Fair Lawn, NJ); ethanol from Quantum Chemical Corp. (Newark, NJ). Phosphate buffer (50 mM, pH 3.0) was prepared by dissolving 6.9 g $NaH_2PO_4 \cdot H_2O$ (HPLC grade, Fisher Scientific) in 1000 ml of USP water. The pH of the buffer was adjusted to 3.0 with 85% *O*-phosphoric acid (HPLC grade, Fisher Scientific).

### 2.2. Instrumentation

The study was performed with a Hewlett–Packard (Agilent, Wilmington, DE) model 6890 series gas chromatograph (total electronic pneumatic control of gas flow) equipped with a capillary split/splitless inlet, a volatiles interface, an HP 7673 automatic liquid sampler, an HP 7694 headspace sampler, and a flame ionization detector (FID). The headspace transfer line was directly connected to the volatiles interface. An auxiliary EPC module was used for vial pressurization. The automatic liquid sampler was attached to the capillary split/splitless inlet. Chromatographic data were collected and handled via the in-house Multichrom chromatographic data management system (Thermo LabSystems, Cheshire, WA, UK).

### 2.3. SHS-GC instrumental conditions

The SHS sampling was performed with the headspace sampler and the volatiles interface. A 1-ml sample loop was employed. The headspace autosampler conditions were as follows: oven temperature, 85 °C; transfer line temperature, 110 °C; loop temperature, 90 °C; vial equilibration time, 40 min; shaking (mixing) speed, high; loop fill time, 0.15 min; injection (or vent) time, 0.3 min; vial pressure, 10 psi; pressurization time, 0.1 min.

A 60 m × 0.53 mm Rtx-1701 column with 1.0 μm film thickness (Restek Corp., Bellefone, PA) was utilized for chromatographic separation of the solvents. The carrier gas was helium at a constant flow rate of 7.0 ml/min. The volatiles interface was maintained at 250 °C with a split ratio of 1:10. The FID was set at 250 °C and nitrogen was used as the make-up gas. The column oven temperature program involved an initial temperature of 50 °C for 3 min, increased at 40 °C/min to 200 °C and held for 1 min.

### 2.4. Direct GC instrumental conditions

Direct liquid sampling was performed with the automatic liquid sampler and the capillary split/splitless inlet. A splitless injection mode was used

with a 1.0-μl injection volume. A 30 m × 0.53 mm DB-WAXetr column with 1.0 μm film thickness (J&W Scientific, Folsom, CA) was used. The carrier gas was helium at a constant flow rate of 4.0 ml/min. The capillary split/splitless inlet was maintained at 140 °C and FID temperature at 260 °C. Nitrogen was used as the make-up gas. The column oven was programmed with an initial temperature of 35 °C for 7 min, increased at 50 °C/min to 200 °C, and held for 20 min.

### 2.5. Standard preparation

Quantification was performed by the method of external standardization. The stock standard solution containing 12.5 mg/ml of each OVI was prepared by diluting 6.25 g each of methanol, ethanol, isopropanol, acetone, and ethyl acetate to 500 ml with sample diluent. The pH 3.0 phosphate buffer in Section 2.1 was used as the diluent for SHS-GC while water or DMF was used for direct GC. The working standard containing 100 μg/ml of each solvent was prepared by diluting 2.0 ml of the stock standard solution to 250 ml with diluent. This concentration of the working standard corresponds to levels that would be obtained by dissolving 200 mg of sample (containing 2500 ppm of each solvent) in 5 ml of diluent. A series of standard solutions for validation was prepared by diluting the stock standard solution with diluent. For SHS-GC analysis, 5.0 ml aliquots of the standard were pipetted into a 20 ml headspace vial and immediately sealed with a Teflon-lined septum and an aluminum crimp cap (Agilent, Wilmington, DE).

### 2.6. Sample preparation

For direct GC analysis, a whole GEM tablet (~200 mg in weight) was crushed and mixed with 5.0 ml of water. The solution was sonicated for 20 min, heated at 60 °C for 1 h, then centrifuged at 14,000 rpm for 30 min. The supernatant layer was transferred into a 2-ml GC vial for analysis.

For SHS-GC analysis, a whole GEM tablet was crushed and transferred into a 20-ml headspace vial. Five ml aliquots of the diluent were transferred into the vial and immediately sealed with a Teflon-lined septum and an aluminum crimp cap. The vial was sonicated for 20 min and loaded onto the headspace sampler for analysis.

## 3. Results and discussion

A typical GC chromatogram of a GEM tablet sample analyzed by the direct injection GC method is shown in Fig. 1. The direct-GC method used was based on the United States Pharmacopoeia (USP) ⟨467⟩ method VI [14]. Fig. 1 illustrates that direct injection of the GEM tablet sample introduced an excessive amount of high boiling point components in the formulation matrix to the column. Poor peak shapes were also observed for the solvents of interest. The method was found to be unsuitable for the determination of residual solvents in the GEM tablet formulations.

### 3.1. SHS-GC method development

#### 3.1.1. Sample preparation

The first step in our SHS-GC method development was to consider the characteristics of both the analytes of interest and the sample. All of the OVIs to be determined: methanol, ethanol, isopropanol, acetone, and ethyl acetate, have sufficient volatility for headspace analysis. De-ionized (DI) water was initially chosen as the sample dissolution medium because it is generally free of organic contaminants and gives no response in a FID (flame ionization detector). However, the gel-forming agent (synthetic high molecular weight polymers of acrylic acid) in the GEM tablet swells in DI water and may introduce a significant matrix effect to the static headspace analysis. It was found that the swelling of the gel-forming agent can be reduced by inhibiting the ionization of acrylic acid at low pH. For this reason, a 50-mM pH 3.0 phosphate buffer used commonly in the HPLC analyses was employed as the sample diluent. It has been suggested by a number of authors that so-called 'salting-out' by saturating the aqueous sample solution with a salt (e.g. $Na_2SO_4$) may reduce the sample matrix effect and increase the sensitivity in the static headspace

analysis [4,5]. The effect of salting-out with the addition of 1 g of $Na_2SO_4$ was examined. Although the sensitivity was enhanced as expected, variability associated with the additional sample preparation resulted in relatively high standard deviations of the headspace determinations. The sensitivity of the method was found to be adequate without the addition of sodium sulfate (see Section 3.2), therefore, salting-out was not utilized for this study. Since fewer steps are required for sample preparation in SHS-GC, the overall analysis time was significantly reduced in comparison with the direct-GC procedure.

### 3.1.2. Chromatographic conditions

The next step was to evaluate the chromatographic conditions. The appropriate choice of GC column is crucial to establish a robust SHS-GC method. The DB-WAXetr column originally used in the direct injection GC method has a very polar polyethylene glycol (PEG) stationary phase and gives poor resolution between isopropanol and ethanol as shown in Fig. 2A. In addition, methanol elutes very closely to ethyl acetate, which was typically observed to be present at a much higher level than methanol, making peak threshold detection and subsequent quantitation of methanol difficult. In an attempt to solve these problems by altering the elution order of methanol and ethyl acetate, DB-1 column coated with a non-polar dimethyl polysiloxane stationary phase was tried. The DB-1 phase is significantly less retentive for polar alcohols than the DB-WAXetr phase as evidenced by the SHS-GC chromatogram shown in Fig. 2B. As a result of the forward shifting of alcohol peaks, all analytes of interest are now well resolved from each other. However, another difficulty was encountered in resolving the methanol peak from a co-eluting sample matrix peak, which was later identified as an acetaldehyde peak. It was suggested that a trace amount of acetaldehyde may be present in the sample solutions due to the hydrolysis or thermal degradation of excipients at elevated temperatures. This is the subject of a separate on-going study. It was noted that the polarity of stationary phases does not have as significant an effect on the elution of acetaldehyde as it does on alcohols. This may be explained by the fact that alcohols exhibit very strong hydrogen bonding

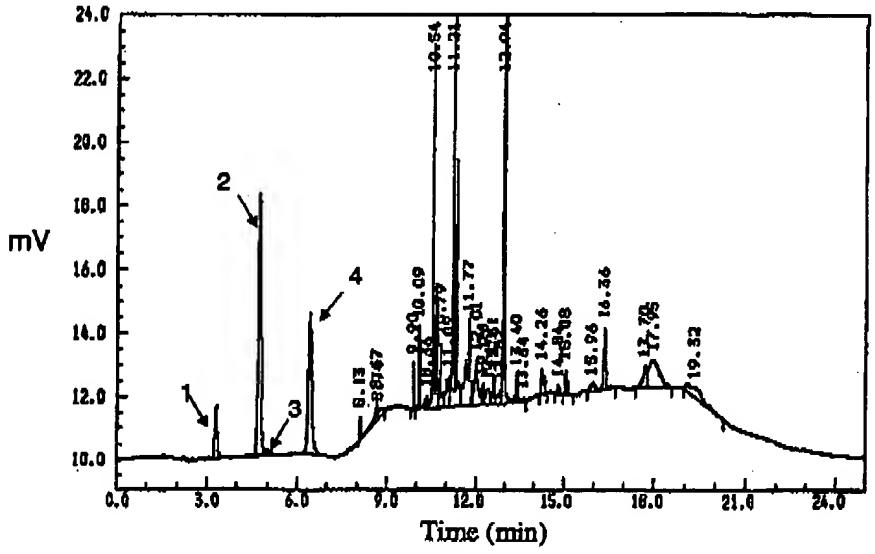


Fig. 1. Typical GC chromatogram of a GEM tablet sample using the direct GC parameters given in Section 2.4. Peaks: 1 = acetone; 2 = ethyl acetate; 3 = methanol; 4 = ethanol.

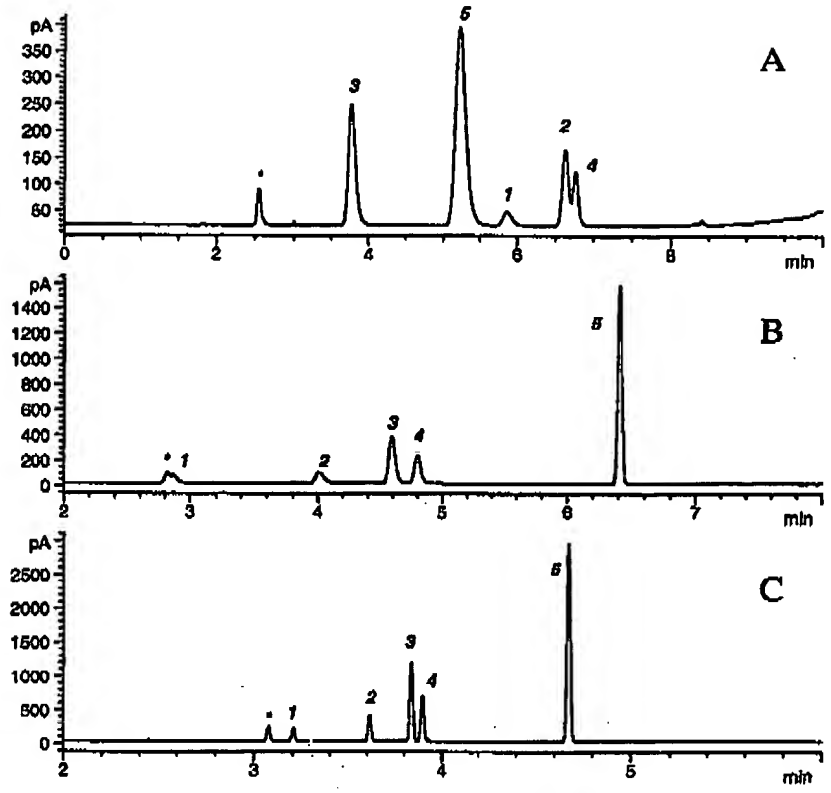


Fig. 2. SHS-GC chromatograms of 100 ppm working standard (see Section 2.5). Method conditions (injector, detector, and headspace sampler conditions given in Section 2.3): (A) J&W DB-WAXetr, 30 m × 0.53 mm I.D., 1.0 μm, carrier gas as He at 35 cm/s measured at 35 °C, column oven temperature 35 °C for 6 min then 35–200 °C at 40 °C/min. (B) J&W DB-1, 30 m × 0.53 mm I.D., 1.0 μm, carrier gas as He at 35 cm/s measured at 35 °C, column oven temperature 35 °C for 6 min then 35–200 °C at 40 °C/min. (C) Restek Rtx-1701, 60 m × 0.53 mm I.D., 1.0 μm, carrier gas as He at 43 cm/s measured at 50 °C, column oven temperature 50 °C for 3 min then 50–200 °C at 40 °C/min then at 200 °C for 1 min. Peaks: 1 = methanol; 2 = ethanol; 3 = acetone; 4 = isopropanol; 5 = ethyl acetate (*, acetaldehyde).

interactions with polar functional groups on polar stationary phases while dispersion is the dominant interaction for acetaldehyde. Acetaldehyde appears as one of the earliest eluting peaks on the liquid stationary phases due to its extremely high volatility. Hence, a stationary phase with an intermediate polarity, such as Rtx-1701 (14% cynopropylphenyl/86% dimethyl polysiloxane), would preferentially retain and separate methanol from acetaldehyde, while maintaining the resolution among other analytes. A 60 m, 0.53 mm I.D. Rtx-1701 column with a 1.0-μm film thickness was then tried. Capillary GC columns with a 0.53 mm I.D., commonly referred to as megabores, are preferred for headspace analysis because they can be operated at higher carrier gas flow rates to reduce peak broadening due to the dead volumes in headspace sampler components. The longer column was chosen in order to obtain a sufficient number of theoretical plates to achieve a satisfactory resolution of all peaks of interest at a relatively high initial GC oven temperature of 50 °C, which would significantly reduce the GC post-run cool-down and re-equilibration time. The combination of a higher flow rate and a higher initial temperature of GC oven resulted in a very short

GC analysis time. The SHS-GC chromatogram obtained with the Rtx-1701 column is shown in Fig. 2C, which illustrates that all peaks of interest are well resolved with excellent peak shapes in less than 5 min. A fast oven temperature ramp to 200 °C was used to elute all unknown or unexpected analytes in actual samples from the GC system. Each SHS-GC run was completed within 10 min compared to the typical 45–60-min run time needed for direct GC analysis [14].

*3.1.3. Optimization of headspace parameters*

There are many instrumental parameters of headspace sampler that can affect the sensitivity, precision, and accuracy of static headspace analysis. These include temperatures (oven, transfer line, and loop); time (vial equilibration and pressurization, loop fill, and injection); pressure (vial and carrier gas), phase ratio (vial size and sample volume), and shake (mixing) speed. Optimization of all parameters would require extensive and lengthy method development. Brillante et al. [7] have determined the optimum instrumental conditions for the determination of five OVIs in bulk pharmaceutical chemicals using the HP 7694 headspace sampler coupled with the HP 6890 Series GC. These parameter settings with the exception of the oven temperature and vial equilibration time were adopted in this study. An 85 °C oven temperature, which is the maximum temperature allowed for an aqueous sample solution, was selected. The higher oven temperature in conjunction with the 'mixing' option on the HP 7694 headspace sampler, which provides vigorous agitation of sample vials during heating, ensures the rapid extraction of residual solvents from GEM tablet formulations. The optimal vial equilibration time was determined by experiments. A 100 ppm working standard was used for the study. The equilibration time was varied from 0 to 90 min and the other parameters were maintained at the same conditions as listed in Section 2.3. Fig. 3 shows the response of the OVIs of interest as a function of vial equilibration time. The results indicate that the equilibrium was reached at 20 min for all analytes. Ethyl acetate exhibits a much higher response due primarily to its more favorable partition coefficient for transfer to the vial headspace from the aqueous matrix compared with other more polar analytes. A 40-min vial equilibration time was chosen to achieve better precision and also to ensure the complete extraction of solvents from GEM tablets. The additional time for vial equilibration does not significantly increase the analysis time, which is limited by the GC run time only since the HP 7694 headspace autosampler allows the staggering of the start of the incubation time.

The final method conditions are given in Section 2.3. Representative SHS-GC chromatograms of the diluent blank, 100 ppm working standard, and sample using these optimized conditions are illustrated in Fig. 4. All analytes of interest are well resolved from each other as well as from all formulation matrix peaks. No significant carryover was observed for each analyte. Compared with the chromatogram obtained using direct injection method (Fig. 1), static headspace sampling introduced only a trace amount of high boiling point components to the chromatographic system. Since little sample preparation is required and the GC run time is very short, the entire SHS-GC assay can be carried out within 3 h. In contrast, an assay by the direct-GC normally requires a total analysis time of more than 8 h.

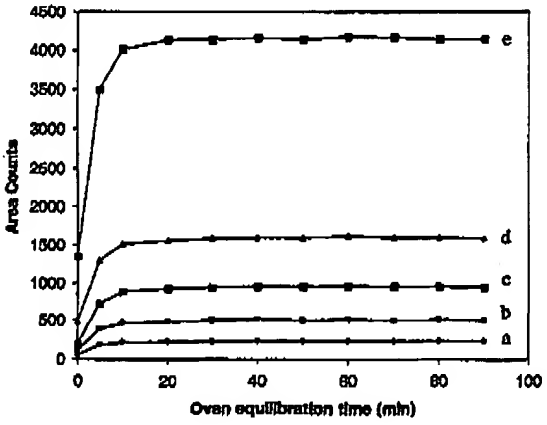


Fig. 3. Plots of oven equilibration time versus peak area: (a) methanol; (b) ethanol; (c) isopropanol; (d) acetone; (e) ethyl acetate.

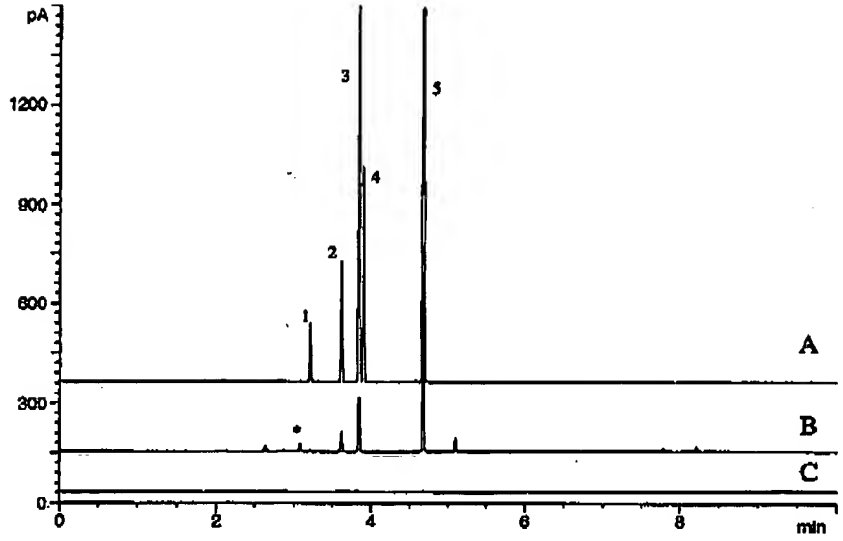


Fig. 4. SHS-GC chromatograms for analysis of residual solvents in GEM tablets. Method conditions are shown in Section 2.3. (A) The 100 ppm working standard (see Section 2.5). (B) A sample of GEM tablet. (C) The diluent blank. Peaks: 1 = methanol; 2 = ethanol; 3 = acetone; 4 = isopropanol; 5 = ethyl acetate (* acetaldehyde).

### 3.2. SHS-GC method validation

The SHS-GC method was validated with respect to linearity, range, detection and quantitation limits, precision, and accuracy in accordance with the International Conference on Harmonization (ICH) guideline Q2B 'Validation of Analytical Procedures: Methodology' [15].

The linearity of the method was evaluated from triplicate injections of a series of standard solutions prepared over the concentration range listed in Table 1 for each OVI. The concentration range for each of methanol, ethanol and isopropanol was from 0.5 to 200% of the working standard, which contains 100 μg/ml of each analyte. Using a 200-mg sample, the range is equivalent to 12–5000 ppm by mass of each OVI in the GEM tablet. The concentration range for both acetone and ethyl acetate was from 0.1 to 200% of the working standard (2.5–5000 ppm by mass of each OVI in the GEM tablet). Results for linearity are summarized in Table 1 along with the estimated detection limits (DLs). Each solvent showed excellent linear behavior over the examined concentration range with coefficient of determination ($R^2$) values of 0.9989–0.9999. The DLs were determined based on the standard deviation ($\sigma$) of the blank and the slope ($S$) of the calibration curve ($DL = 3.3\sigma/S$) as defined in the ICH guideline [15]. The DLs are determined as 3 ppm for methanol, 2 ppm for both ethanol and isopropanol, and 1 ppm for both acetone and ethyl acetate, indicating the superb sensitivity of the SHS-GC method. The lower end of the linear range is defined as the quantitation limit (QL) for

Table 1
Linear ranges and estimated detection limits for SHS-GC method

| OVIs | Concentration[a] range (ppm) | $R^2$ | DL[b] (ppm) |
|---|---|---|---|
| Methanol | 12–5000 | 0.9992 | 3 |
| Ethanol | 12–5000 | 0.9996 | 2 |
| Isopropanol | 12–5000 | 0.9989 | 2 |
| Acetone | 2.5–5000 | 0.9996 | 1 |
| Ethyl acetate | 2.5–5000 | 0.9999 | 1 |

[a] Concentration expressed on a weight basis relative to a 200 mg sample weight.
[b] DL = 3.3 × (SD of blank)/(slope of calibration curve).

Table 2
Accuracy and precision for SHS-GC method

| OVIs | Chromatographic precision[a] RSD (%) | Recovery[b] (%) | Method precison[c] RSD (%) |
|---|---|---|---|
| Methanol | 2.6 | 93–99 | 3.5 |
| Ethanol | 2.0 | 87–98 | 1.9 |
| Acetone | 0.8 | 85–102 | 1.1 |
| Isopropanol | 1.2 | 93–100 | 1.6 |
| Ethyl acetate | 0.4 | 87–107 | 0.6 |

[a] Determined from ten replicate injections of 100 ppm standard solution.
[b] Determined by spiking samples with standards over the linearity range. Recoveries are within 93–107% over the linear range above the QL.
[c] Determined from b.

each analyte, i.e. 12 ppm each for methanol, ethanol, isopropanol, and 2.5 ppm for both acetone and ethyl acetate.

The accuracy of the method was validated by spiking GEM tablet formulations with standards prepared at the levels over the linear range specified in Table 1 for each OVI. Triplicate determinations were performed at each level. Results are summarized in Table 2 along with chromatographic precision data, which were obtained from ten replicate injections of the working standard. The relative standard deviations (RSDs) of ten replicates for all solvents are equal to or less than 2.6%, which is well below the USP mandated limit of 15% RSD for OVI analysis [14]. Recoveries obtained for each of the analytes are within 85–110% (within 93–107% over the linear range above the QL and within 85–110% at the QL), demonstrating sufficient accuracy for trace analysis. The method precision was assessed in combination with the accuracy study. RSDs of 3.5% or less of the recovery data in triplicate indicate that the SHS-GC method provides excellent precision for residual solvent analysis.

Table 3
Extraction of residual ethanol and acetone from polymeric coating

| OVIs | SHS-GC[a] (%) | Direct injection GC[b] (%) |
|---|---|---|
| Ethanol | 1.25 | 1.36 |
| Acetone | 0.45 | 0.46 |

[a] Active ingredient and excipients of core tablet were added to the polymeric coating sample to match the formulation matrix.
[b] DMF used to dissolve the polymeric coating sample.

Since the polymeric coating of the GEM tablet is insoluble in water, the extraction of ethanol and acetone into the sample dissolution medium from the coating was further investigated. In this experiment, a coating sample was collected by separating the coating from the GEM tablet core. The sample was then analyzed using both the SHS-GC method and the direct GC method to determine the ethanol and acetone content in the polymeric coating and the results were compared. DMF was used to dissolve the polymeric coating for the direct GC determination. For the headspace analysis, other components of the GEM tablet were also added to match the formulation matrix. The comparative results are given in Table 3, which indicates that the SHS-GC procedure was sufficient to fully extract residual ethanol and acetone from the polymeric coating.

Based on the above validation results, the SHS-GC procedure has been demonstrated to provide an acceptable degree of accuracy and precision within or at the extremes of the linear range. Therefore, the range of the method has been determined as follows: 12–5000 ppm each for methanol, ethanol, and isopropanol; 2.5–5000 ppm for both acetone and ethyl acetate, in reference to a 200-mg GEM tablet.

## 4. Conclusions

A static headspace gas chromatographic method was developed for the determination of

residual methanol, ethanol, acetone, isopropanol, and ethyl acetate in pharmaceutical gel extrusion module (GEM) tablet formulations. A Rtx-1701 megabore capillary column was found to provide the optimal chromatography for the headspace analysis. Utilization of a low pH buffer minimized the matrix effect of the GEM formulation. The SHS-GC method has been shown to be specific, sensitive, precise, and accurate. In addition, the automated SHS-GC procedure is simple and rapid. This study demonstrates that static headspace analysis is an ideal approach for the analysis of residual solvents in complex pharmaceutical products. It minimizes the possibility of chromatographic system contamination as well as artifact formation. Furthermore, it substantially reduces routine maintenance of the GC system. Most importantly, the SHS-GC method provides much more accurate and precise quantitation results than the direct GC method.

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1995



1: J Chromatogr Sci 1995 Jan;33(1):49-54 Related Articles, NEW Links



# Factors that influence the determination of residual solvents in pharmaceuticals by automated static headspace sampling coupled to capillary GC-MS.

**Mulligan KJ, McCauley H.**

National Forensic Chemistry Center, U.S. Food and Drug Administration, Cincinnati, Ohio 45202.

The impact of several experimental parameters on static headspace sampling for volatile impurities is discussed. Figures of merit are provided for some common organic solvents dissolved in dimethylacetamide. The performance is compound specific, but in the best case, detectability is about 0.2 mg/L with the mass spectrometer operating in the scanning mode. Sensitivity improves by about a factor of 50 when single ion monitoring is used. Linearity extends for about 4 orders of magnitude. This system is used to determine acetone as a residual solvent in the sulfonamide antibiotic, sulfamethazine, at levels of 1 to 15 mg/kg with precision of 3 to 5%.

PMID: 7852481 [PubMed - indexed for MEDLINE]



200 µg/L

4 µg/L

9
6
11/7



# Improved determination of organic volatile impurities in pharmaceutical materials by (USP-467) using automated static headspace GC/MS.

**McClure GL.**

Perkin Elmer Corporation, Wilton, Connecticut, USA.

PMID: 10754702 [PubMed - indexed for MEDLINE]

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1: J Pharm Biomed Anal 1998 Dec;18(4-5):623-38 Related Articles, NEW Links

# Residual solvents determination in pharmaceutical products by GC-HS and GC-MS-SPME.

**Camarasu CC, Mezei-Szuts M, Varga GB.**

Gedeon Richter Ltd., Central Analytical Laboratory, Budapest, Hungary. costin@orthodox.com

Solid-phase microextraction (SPME) has been applied to the residual solvents determination in pharmaceutical products and was compared with the static headspace. Three fibers with different polymer films were compared and the polydimethylsiloxane/divinylbenzene coated fiber was found to be the most sensitive for the analyzed analytes. Between the investigated sample preparation techniques, gastight-SPME proved to be the most sensitive, with DL values ranging from 5 pg ml(-1) to 2 ng ml(-1). Headspace SPME is more precise, with RSD of peak areas values ranging from 2 to 3%. The headspace SPME method was successfully validated. The validation data are reported in the text. The most important difference between the two techniques is that the gastight SPME showed better behavior towards very volatile solvents. Compared with the static headspace technique, both SPME methods showed superior results, being compatible with the pharmaceutical samples.

PMID: 9919963 [PubMed - indexed for MEDLINE]

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## Gas chromatography.

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Publication Types:
- Review
- Review, Academic

PMID: 8092480 [PubMed - indexed for MEDLINE]